23

Partial Liquid Ventilation in the Extremely Preterm Infant: Potential Benefits and Harms

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1. Introduction

Preterm infants, especially the extremely preterm, require a large amount of support *ex utero*. They are often critically ill with greatly reduced chances of survival. Many die because of their overall immaturity with multiple organ systems that cannot adjust to extrauterine life, especially the lungs. Many die from their primary lung disease. The respiratory support they get from positive pressure ventilation almost always causes significant secondary lung injury.

Over the previous decades partial liquid ventilation has been put forward as an adjunct form of respiratory support for especially immature lungs and severe lung disease: not only to provide a superior form of respiratory support but to deliver that support with reduced lung injury. Recent studies have renewed the hope that partial liquid ventilation has great potential to change the course of neonatal lung disease and respiratory morbidity. (Blassnig, 2009)

Unfortunately, the extremely preterm infant is also at great risk of particular forms of brain injury (e.g., intraventricular haemorrhage, periventricular leucomalacia and other white matter injury). Disturbance of cerebral blood flow has been demonstrated to considerably increase the risk of these forms of brain injury.

One of the concerns with using partial liquid ventilation in the extremely preterm infant is its affect on cerebral blood flow which could lead to brain injury, especially at the start of partial liquid ventilation during the initial dosing of perfluorocarbon into the lungs. Any benefits of partial liquid ventilation might be outweighed by an increased risk of brain injury and the subsequent devastating consequences.

Before using partial liquid ventilation in human preterm infants it should be known to be safe with regard to its effects on cerebral blood flow during perfluorocarbon dosing. The effect of perfluorocarbon dosing at the start of partial liquid ventilation on cerebral blood flow can be mitigated to minimise or eliminate these adverse effects.

2. The consequences of lung disease in the extremely preterm neonate

2.1 Mortality

The extremely preterm infant, born at less than 26 weeks gestational age, is at great risk of dying. The risk increases with decreasing gestational age. The majority of these infants die because of general immaturity (including extremely immature lungs) or lung disease.

Data are available from Australia and New Zealand. All babies that are admitted to a newborn nursery who were born at less than 32 completed weeks gestation, or weighed <1,500 grams at birth, or received assisted ventilation (mechanical ventilation), or received major surgery are registered with the Australian and New Zealand Neonatal Network (ANZNN). The ANZNN reports annually on all registered babies. (ANZNN, 2009) The latest report of the ANZNN (ANZNN, 2009) is for births in 2006; of 339,271 live births there were 7,592 registered babies (2.2% of live births). There were 412 registered babies born at <26 weeks gestational age (5.4% of registered babies). Two thirds (276/412) survived to be discharged home – a mortality of 33%.

The EPICure study (Wood, 2000) is a large population based study designed to reveal outcomes for extremely preterm infants. They enrolled all babies born at less than 26 weeks gestational age, from March 1995 to December 1995, who were admitted to a neonatal intensive care unit in the United Kingdom of Great Britain and Northern Ireland and the Republic of Ireland. These infants are deemed to be extremely immature and at the limits of viability. About sixty percent (60%) of these infants died before discharge from hospital and about 70% of those deaths had a respiratory cause. (Costeloe, 2000) In an Australian study from around the same period (1992-1996) at the Royal Women's Hospital in Melbourne, about 28% of live born infants of 23 to 27 weeks gestational age died. Of those infants admitted to the intensive care nursery 60% of deaths had a respiratory cause. (Doyle, 1999)

Recent data are available from the Royal Brisbane and Women's Hospital in Brisbane, Australia. From 2003-2007 inclusive there were 163 infants admitted of less than 26 weeks gestational age: 58 (36%) died. Sixty-two percent (62%) of those deaths were either due to 'extreme prematurity' or a direct respiratory cause. (Cartwright, 2003; Cartwright, 2004; Cartwright, 2005; Cartwright, 2006; Cartwright, 2007)

2.2 Respiratory morbidity

Lung immaturity and/or lung disease not only carries a high mortality in extremely preterm babies, but it also causes significant morbidity. This includes the requirement for respiratory support, air leak and neonatal chronic lung disease. Mechanical ventilation often causes significant secondary lung injury due to barotrauma and volutrauma. This makes the acute lung disease much worse and, along with extreme prematurity, is a major factor in the subsequent progression to chronic lung disease. Neonatal chronic lung disease consists of distortion of the lung architecture, disturbed lung growth and chronic inflammation of the small airways and the lung parenchyma. Most patients with neonatal chronic lung disease are born extremely preterm. Infants with chronic lung disease have significant morbidity which manifests as a requirement for prolonged respiratory support and oxygen therapy, as well as an increased hospital stay. Chronic lung disease is also a major cause of late mortality.

Many extremely preterm infants need mechanical ventilation. About ninety percent (90%) of ANZNN registered babies in 2006 required some form of assisted ventilation. (ANZNN, 2009) The mean length of time of assisted ventilation was 11 days. Most babies required respiratory support for either hyaline membrane disease or non-specific respiratory distress. Intubation and positive pressure mechanical ventilation was required by ninety-seven percent (97%) of babies born <26 weeks gestation. The most extreme form of acute lung injury in ventilated neonates is air leak (pneumothorax, pulmonary interstitial emphysema, pneumomediastinum); it occurred in eight percent (8%) of infants <26 weeks gestational age.

The ANZNN defines chronic lung disease as any registered baby born less than 32 weeks gestational age who needs assisted ventilation for their initial lung disease and continues to require some form of respiratory support or oxygen therapy at 36 weeks corrected gestational age. Of babies born less than 26 weeks gestational age, who survived to 36 weeks corrected gestational age, 55% had chronic lung disease. Four percent (4%) of surviving registered babies born less than 32 weeks gestational age required prolonged oxygen therapy and went home on oxygen treatment. (ANZNN, 2009)

Local data from the Royal Brisbane and Women's Hospital (Cartwright, 2003; Cartwright, 2004; Cartwright, 2005; Cartwright, 2006; Cartwright, 2007) from 2003 to 2007 inclusive for 163 infants admitted of less than 26 weeks gestational age showed that:

- 99% were intubated and ventilated;
- the mean length of time of ventilation was 36 days (2001-2007 data only);
- 27% had an air leak;
- 74% had chronic lung disease; and
- 16% went home on oxygen treatment.

Three quarters (74%) of the EPICure cohort (Hennessy, 2008) had moderate to severe chronic lung disease; 36% went home on oxygen treatment. By two years of age almost two thirds of the cohort required hospital admission at least once for a respiratory illness. At six years many of the cohort had continuing respiratory symptoms, abnormal respiratory findings on physical examination and/or abnormal respiratory function tests.

2.3 Non-respiratory morbidity

Non-respiratory morbidity is very common in extremely preterm infants. This includes a number of different organ systems. The major morbidities include patent ductus arteriosus, necrotising enterocolitis, retinopathy of prematurity, intraventricular haemorrhage and periventricular leucomalacia.

Extremely preterm infants that survive also require a prolonged hospital stay (even when this is not because of respiratory disease). The long-term sequelae of extreme prematurity can include adverse neurodevelopmental outcomes such as developmental delay, cognitive and learning impairment, cerebral palsy, blindness and deafness.

Local data from the Royal Brisbane and Women's Hospital from 2003 to 2007 inclusive (Cartwright, 2003; Cartwright, 2004; Cartwright, 2005; Cartwright, 2006; Cartwright, 2007) shows that of the 163 infants admitted of less than 26 weeks gestational age:

- 61% had a patent ductus arteriosus;
- 46% had an intraventricular haemorrhage and/or periventricular leucomalacia;
- 16% had a severe intraventricular haemorrhage;
- 57% had retinopathy of prematurity (20% had severe retinopathy of prematurity); and
- the average length of stay in hospital was 127 days.

2.4 Mechanical ventilation

The management of lung disease in extreme preterm infants is predicate on the principle that respiratory support be provided until there is sufficient resolution of the lung disease and respiratory support is no longer required. Mechanical ventilation is a means of providing such support for babies with severe lung disease or extreme prematurity. Ventilation is provided to support gas exchange, i.e., oxygenation and carbon dioxide clearance.

The types of mechanical ventilation include-

1. Conventional mechanical ventilation – pressure controlled, time-cycled ventilation, including:
   - intermittent positive pressure ventilation;
   - synchronised intermittent positive pressure ventilation;
   - volume-targeted ventilation.
2. High frequency ventilation.
3. Volume-controlled ventilation – rarely used in neonates.

As can be seen from the above data the more usual forms of mechanical ventilation often don't work (babies still die from their extremely immature lungs and lung disease) and often damage the lungs causing significant respiratory morbidity (lung injury and subsequent chronic lung disease).

There is still a need for alternative forms of respiratory support that can provide ventilation and adequate gas exchange without damaging the lungs or put the infant at increased risk of brain injury.

3. The risk of brain injury in the extremely preterm infant

The developing brain is especially prone to injury and extremely preterm infants are at significant risk; this can result in long-term disability. (Vohr, 1996) The most common forms of brain injury arising in preterm infants are intraventricular haemorrhage, periventricular leukomalacia and other forms of white matter injury. Disturbance of cerebral blood flow have been demonstrated to substantially increase the risk of brain injury.

The germinal matrix lies in the subependymal region at the floor of the lateral ventricle and this is the site of intraventricular haemorrhage. It is especially prone to both under perfusion and over perfusion. The vascular structure of this region predisposes to damage from ischaemia and later reperfusion and/or over perfusion with subsequent venous haemorrhage. (Takashima, 2009) With severe grades of intraventricular haemorrhage there is additional haemorrhage in the periventricular white matter; both focal injury and more diffuse white matter injury. The white matter is especially susceptible because of the vulnerability of the glia (especially premyelinating oligodendrocytes) which is gestational age dependant. Also the periventricular area has a blood supply which is immature and watershed. The white matter is also particularly prone to hypoperfusion. (Takashima, 2009; Volpe, 2009a; Volpe, 2009b)

Given the vulnerability of the brain of the extremely preterm infant to both under and over perfusion it is not surprising that fluctuations of cerebral blood flow cause the most overt types of brain injury. (Ballabh, 2010; Perlman, 2009) Factors that lead to low cerebral blood flow also increase the risk of intraventricular haemorrhage and similarly those factors that lead to increased cerebral blood flow also increaese the risk of intraventricular haemorrhage. (Bassan, 2006) Periventricular leucomalacia can be easily produced in animal models of cerebral ischaemia. (Yoshioka, 1994; Ohyua, 1999)

Increased cerebral blood flow velocity increases the incidence of intraventricular haemorrhage and extension of existing intraventricular haemorrhage. (Van Bel, 1987) Low cerebral blood flow states increase the risk of intraventricular haemorrhage. (Kluckow 2000; du Plessis, 2008) The strongest link exists with the development of intraventricular haemorrhage and more variability in cerebral blood flow. (Vohr, 1996; Van Bel, 1987; Mullaart; 1994, Kissack, 2004; Perlman, 1983; Takashima 1995) In the beagle pup model

rapid changes in cerebral perfusion easily produce subependymal haemorrhages indistinguishable from those seen in human preterm infants. (Ment, 1982) Keeping cerebral blood flow fluctuations to a minimum must be a prime aim when caring for extremely preterm infants to prevent intraventricular haemorrhage. (du Plessis, 2008; Wells, 1995)
There are many factors that are known to alter cerebral blood flow in newborn infants (see Table 1). Because the preterm infant is more likely to have all the conditions listed in the left hand column of Table 1 it is not unreasonable to presume that fluctuations in cerebral blood flow are common particularly in the first few days of life. The preterm infant may also experience wide variations in cerebral blood flow because they do not have the normal autoregulation of cerebral blood flow. Thus periods of pressure-passive cerebral circulation are likely; the fluctuations in blood pressure that are common (Coughtrey, 1997) expose them to the extremes of cerebral blood flow and put them at risk of intraventricular haemorrhage. (du Plessis, 2008)

Factor	**Effect**
Cerebral perfusion pressure	**increased** perfusion pressure **increases** CBF … and vice versa
- arterial BP	- **increased** arterial pressure **increases** CBF … and vice versa
- venous pressure	- **decreased** venous pressure **increases** CBF … and vice versa
$PaCO_2$	**increased** $PaCO_2$ **increases** CBF … and vice versa
PaO_2	**increased** PaO_2 **increases** CBF … and vice versa
Patent ductus arteriosus	PDA with Left-to-Right shunt **decreases** diastolic flow which **decreases** CBF
Hypoglycaemia	**decreased** blood glucose **increases** CBF
Haemoglobin/blood viscosity	**increased** viscosity **decreases** CBF … and vice versa
Posthypoxic-ischaemic injury	vaso-dilatation **increases** CBF
Brain metabolism/activity	**increased** activity **increases** CBF … and vice versa
Autonomic nervous system	**increased** parasympathetic drive **increases** CBF … and vice versa **decreased** sympathetic drive **increases** CBF … and vice versa
Temperature	mild-moderate hyperthermia **increases** CBF hypothermia **decreases** CBF

Table 1. Factors known to alter cerebral blood flow. (Perlman, 2009; Pryds, 1996; Ito, 2005; Vavilala, 2002; Greisen, 2005; Volpe, 1982; Leahy, 1980; Rahilly, 1980) (CBF – cerebral blood flow; BP – blood pressure; CVP – central venous pressure; $PaCO_2$ – arterial carbon dioxide; PaO_2 – arterial oxygen; PDA – patent ductus arteriosus)

Many of the mechanisms listed in Table 1 put the extremely preterm infant at serious risk of significant cerebral blood flow alterations and intraventricular haemorrhage. Many respiratory problems or treatments are known to alter cerebral blood flow and/or increase the risk of intraventricular haemorrhage. These include:

- intratracheal surfactant instillation (has been shown to increase or decrease cerebral blood flow velocity on Doppler ultrasound (Schipper, 1997; Saliba, 1994; Kaiser, 2004);

- asynchronous breathing mechanical ventilation (increases the variability of cerebral blood flow (Rennie, 1987);
- endotracheal tube suction (has been shown to increase or decrease cerebral blood flow on near infrared spectroscopy (Limperopoulos, 2008;, Perlman, 1983; Kohlhauser, 2000);
- endotracheal tube retaping increases cerebral blood flow on near infrared spectroscopy (Limperopoulos, 2008);
- pneumothorax increases cerebral blood flow velocity on Doppler ultrasound, and increases the incidence of intraventricular haemorrhage. (Hill, 1982; Mehrabani, 1991)

The alterations in cerebral blood flow during the administration surfactant are of particular concern because surfactant administration is comparable to the intratracheal administration of perfluorocarbon when starting partial liquid ventilation. Any perfluorocarbon administration effects on cerebral blood flow may increase the risk of brain injury in the extremely preterm infant.

4. Liquid ventilation

Extremely preterm infants with immature lungs and severe lung disease could benefit greatly from alternative forms of respiratory support. New techniques are required because conventional forms of mechanical ventilation often don't work (babies still die from their extremely immature lungs and lung disease) and often damage the lungs causing significant respiratory morbidity (lung injury and subsequent chronic lung disease).

Liquid ventilation has been touted as an alternative form of respiratory support for numerous and varied types of lung disease. Extremely preterm infants with immature lungs and severe lung disease could benefit greatly from the technique of partial liquid ventilation. Recent studies have renewed the promise that partial liquid ventilation has significant potential to alter the course of neonatal lung disease and respiratory morbidity. (Blassnig, 2009)

4.1 History

Artificial respiration using liquid ventilation in mammals was initially tried in mice in the 1960s with solutions of saline in a hyperbaric environment. (Kylstra, 1962) Later experiments in the 1960s showed the successful use of fluorocarbons at atmospheric pressure for liquid ventilation in mice and cats. (Clark, 1966) At first experiments with perfluorocarbons were performed with immersion in perfluorocarbon liquid with spontaneously breathing animals or with gravity-assist bulk tidal flow of perfluorocarbon liquid. These techniques were not successful at removing sufficient carbon dioxide. (Kylstra, 1966; Schoenfish, 1973; Shaffer, 1978) Over the ensuing decades the use of time-cycled, pressure-limited mechanical ventilators allowed the development of the method of total liquid ventilation. (Shaffer, 1975) Total liquid ventilation can maintain adequate gas exchange in animals. (Wolfson, 1990) It has also been shown to improve lung function and gas exchange in experimental animal models of respiratory distress. (Shaffer, 1976; Shaffer, 1984; Shaffer, 1983; Wolfson, 1992) In 1991 Fuhrman *et al*. (Fuhrman, 1991) introduced the method of perfluorocarbon associated gas exchange using functional residual capacity volumes of perfluorocarbon with conventional gas ventilation. This technique is now best known as partial liquid ventilation and it is this technique which is most promising for practical clinical application.

4.2 Partial liquid ventilation

The technique of partial liquid ventilation entails pouring perfluorocarbon liquid into the endotracheal tube whilst ventilating the lung with gas ventilation (either conventional or high-frequency) continues. Customarily the starting volume of perfluorocarbon instilled into the lungs equals the estimated functional residual capacity and the perfluorocarbon is usually given slowly over 10 to 20 minutes. Repeated doses of perfluorocarbon are then given at intervals to keep a fluid level in the endotracheal tube at a positive end expiratory pressure (PEEP) of zero. Repeat doses are necessary because the functional residual capacity will increase as the liquid recruits collapsed alveoli, and to replace losses due to evaporation. Stopping partial liquid ventilation is achieved by ceasing further instillation of perfluorocarbon to allow it to evaporate into the expired gases. The technique is the same when used with high-frequency ventilation.

Perfluorocarbon liquids are a group of chemicals that are formed from the fluorination of organic compounds such as alkanes. They are odourless and colourless, and are chemically and biologically inert. Perfluorocarbons are almost insoluble in lipid and insoluble in water. They are more dense than water and soft tissue. Perfluorocarbon liquids can dissolve more than 20 times the oxygen, and three times the carbon dioxide, than water. They have a low surface tension and low viscosity, and most evaporate faster than water. (Shaffer, 1992; Degraeuwe, 1995)

The physical characteristics of perfluorocarbon liquids (see Table 2) determine the effects of partial liquid ventilation (Figure 1). During normal breathing and gas ventilation the inert gas nitrogen carries oxygen and carbon dioxide. During liquid ventilation perfluorocarbon replaces nitrogen as the carrier of oxygen and carbon dioxide. Perfluorocarbon liquids have a high oxygen carrying capacity and high solubility for carbon dioxide. (Shaffer, 1992; Meaney, 1997) The perfluorocarbon liquid is oxygenated and carbon dioxide removed by means of bulk tidal flow of gas provided by the gas ventilator. This occurs for either conventional or high frequency ventilation. The movement of perfluorocarbon in small peripheral airways is facilitated by its low viscosity.

The surface tension of perfluorocarbon liquids is low, (Shaffer, 1992) at around 15 to 18 millinewton per metre (mN/m). When the perfluorocarbon liquids goes into the lung the air/liquid alveolar interface (which in surfactant deficiency has a high surface tension of up to 50 mN/m (von Bismarck, 2007)) is abolished and surface tension decreases. This increases compliance and therefore alveolar recruitment improves. This allows the use of lower ventilator pressures and smaller tidal volumes; with reduction of barotrauma and volu-trauma respectively. Perfluorocarbons do not disturb natural surfactant production (Cleary, 1997) and they do not wash surfactant out of the lungs. (Rüfer, 1970; Modell, 1970)

Compared to water and soft tissue perfluorocarbon liquids have a high density (Shaffer, 1992) and will therefore mechanically recruit collapsed alveoli. This happens preferentially in the dependant portions of the lung therefore decreasing intra-pulmonary shunting by improving ventilation/perfusion matching. (Kelly, 1997)

Partial liquid ventilation has been known to have some anti-inflammatory effects. These were thought to be due mainly to the less injurious nature of liquid ventilation. However, it is now clear that perfluorocarbons have some direct anti-inflammatory action on cells (such as alveolar macrophages). Also this direct anti-inflammatory effect goes further than the perfluorocarbons acting as a simple barrier. (Heard, 2000) There is direct inhibition of the inflammatory response of alveolar macrophages in contact with perfluorocarbon liquids. (Smith, 1995; Thomassen, 1997) A recent study has shown that the disruption of lung

development in newborn rats, caused by hyperoxia, can be prevented by a single daily dose of perfluorocarbon liquid into the lungs. (Blassnig, 2009)

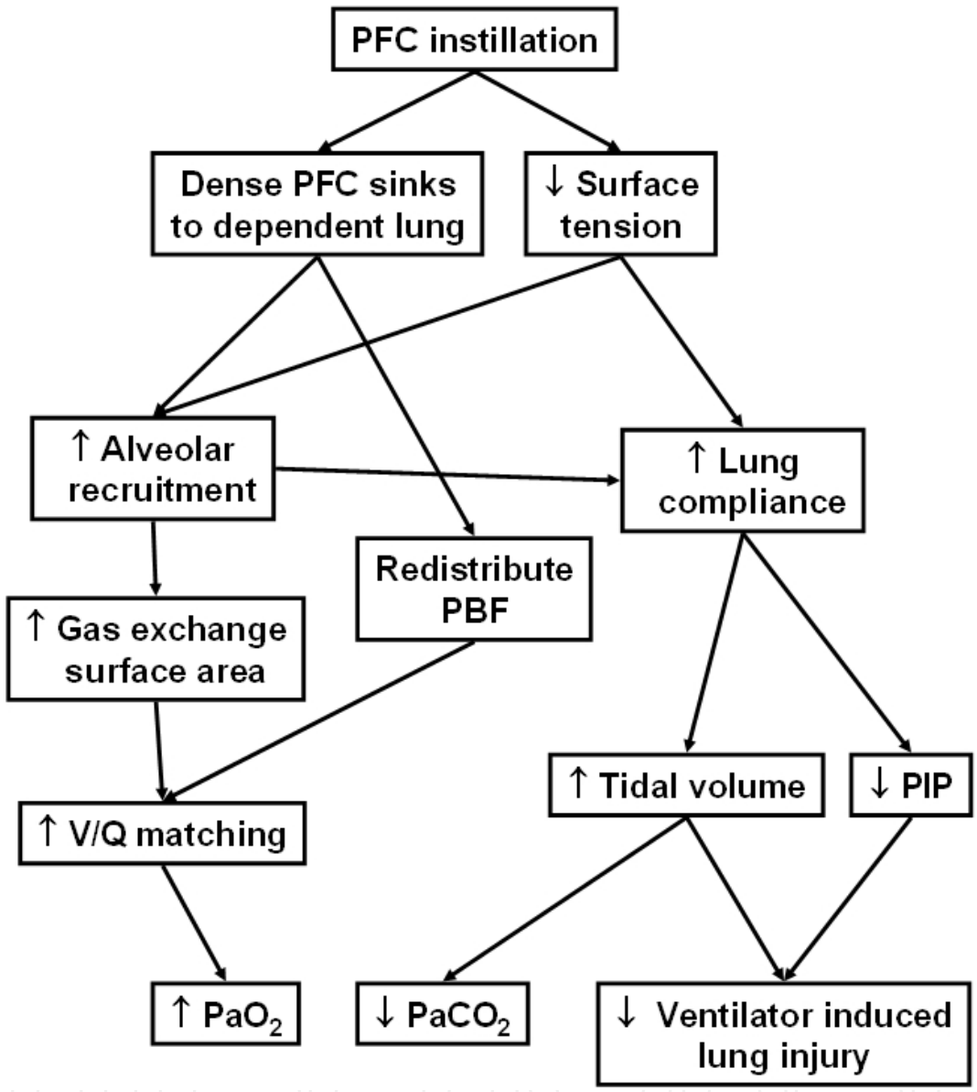

Fig. 1. The mechanical effects of partial liquid ventilation on respiratory function. (Davies, 2011) ($PaCO_2$ – arterial carbon dioxide; PaO_2 – arterial oxygen; PBF – pulmonary blood flow; PFC – perfluorocarbon; PIP – peak inspiratory pressure; Q – perfusion; V –ventilation)

4.3 Animal studies

Partial liquid ventilation has been touted as an alternative form of respiratory support for many types of lung disease because it improves gas exchange and lung function in the diseased and injured lung. Many animal studies using various models of lung injury and surfactant lack have shown improvement in oxygenation, carbon dioxide clearance and lung compliance. (Foust, 1996; Tutuncu, 1993; Smith, 1997a; Leach, 1993; Leach, 1995; Curtis, 1994a; Curtis, 1994b) Partial liquid ventilation is more effective in improving gas exchange and lung function than surfactant alone. (Leach, 1995) There is significantly less damage on

lung histology to lungs after partial liquid ventilation. (Foust, 1996; Smith, 1997a) Lower peak inspiratory pressures can be used to achieve adequate tidal volumes. (Degraeuwe, 1996) Partial liquid ventilation decreases intra-pulmonary shunting. (Zobel, 1996) Partial liquid ventilation increases oxygenation when combined with nitric oxide when treating pulmonary hypertension. (Zobel, 1996)

Most of the above studies have shown benefits of partial liquid ventilation over a few hours. Two studies have shown that it is feasible to use partial liquid ventilation for longer periods. Neonatal piglets with normal lungs have been ventilated for 24 hours with stable ventilation and blood gases with no haemodynamic deterioration. (Salman, 1995) Newborn piglets with surfactant deficiency demonstrated improved oxygenation and lung histology with up to 20 hours of partial liquid ventilation. (Smith, 1997a)

	Saline	**FC-77**	**Perflubron**
Density (g/mL)*	1.0	1.78	1.93
Kinematic viscosity (centistokes)*	1.0	0.8	1.10
Vapour pressure (mmHg)†	47	85	11
Surface tension (mN/m)*	72	15	18
Oxygen solubility (mL/100 mL)*	3.0	50	53
Carbon dioxide solubility (mL/100 mL) †	57	198	210

Table 2. Physical properties of two perfluorocarbon liquids compared with saline.
(* 25°C; †37°C)

Partial liquid ventilation has also been used with high frequency ventilation. Animal studies investigating the effects of partial liquid ventilation with high frequency ventilation have shown the combined technique provides good gas exchange. (Smith, 1997a; Baden, 1997, Mrozek, 1998; Smith, 1997b; Sukumar, 1998) Smith *et al*. (Smith, 1997b) comparing various methods of high frequency partial liquid ventilation, showed that those forms of high frequency ventilation which allow volume recruiting manoeuvres, such as the addition of intermittent conventional breaths, gave superior gas exchange. It seems that, with the use of strategies aimed at maximal alveolar recruitment, high frequency partial liquid ventilation may not confer any additional benefit over high frequency ventilation alone. Davies *et al*. (Davies, 1999) demonstrated that if maximal recruitment is obtained with high frequency ventilation prior to starting high frequency partial liquid ventilation that the addition of partial liquid ventilation did not further improve oxygenation.

4.4 Human studies

4.4.1 Adult

A Cochrane systematic review (Davies, 2004a) of partial liquid ventilation in adults with acute lung injury and acute respiratory distress syndrome found one randomised, controlled trial. (Hirschl, 2002) Another randomised, controlled trial has since been

published. (Kacmarek, 2006) There were no differences, in either study, in any clinically relevant outcomes in patients ventilated with partial liquid ventilation compared with conventional ventilation.

4.4.2 Paediatric

The Cochrane systematic review (Davies, 2004b), updated in 2009, of partial liquid ventilation in children with acute lung injury and acute respiratory distress syndrome found only one randomised, controlled trial as yet unpublished. (Fuhrman, 1998) This trial abstract report showed results from a clinical trial that was stopped early on paediatric acute respiratory distress syndrome (ARDS). The protocol underwent a number of changes during the trial which resulted in three different sets of inclusion criteria. The final set, with liberalised inclusion criteria, had an unexpected decrease in mortality in the control group so the trial was stopped to allow full data analysis to determine the safety of partial liquid ventilation in this group of patients. There were 182 patients enrolled (less than 20% of the target numbers) with an overall mortality of 24/91 (26%) in the partial liquid ventilation group and 18/91 (20%) in the conventional mechanical ventilation group. The authors concluded that partial liquid ventilation with perflubron was safe, however the trial was not powered to detect real differences in mortality and ventilator free days.

4.4.3 Neonatal

There have been several published reports of uncontrolled studies on the use of partial liquid ventilation in human neonates. (Meaney, 1997; Greenspan, 1989; Hirschl, 1995; Pranikoff, 1996; Garver, 1996; Leach, 1996; Bruch, 1997)

Pranikoff *et al*. (Pranikoff, 1996) reported the use of partial liquid ventilation in four infants with congenital diaphragmatic hernia, all of whom were on extra-corporeal life support at the time. There was improved oxygenation and total lung compliance with haemodynamic stability and no acute adverse effects.

Leach *et al*. (Leach, 1996) reported the use of partial liquid ventilation in 13 preterm infants from 24–33 weeks gestational age who had severe respiratory distress syndrome and failing conventional therapy. Ten infants had from 24 to 72 hours of partial liquid ventilation with improvement in oxygenation and lung compliance. Six of the 10 survived to 36 weeks corrected age. The partial liquid ventilation reportedly well tolerated without significant haemodynamic disturbance.

Two randomised controlled trials have been started in newborn infants but both were stopped before reaching their targeted numbers. Both remain unpublished. Hirschl wrote in a review on liquid ventilation of a randomised, controlled trial comparing conventional mechanical ventilation with partial liquid ventilation in preterm infants with severe lung disease. (Hirschl, 2004) Twenty-four patients were recruited to the study: 8 of 13 (62%) in the partial liquid ventilation group survived and all in the conventional ventilation group survived. Hirschl wrote that "This study was placed on hold concomitant with discontinuation of the paediatric trial and has not been resumed." (Hirschl, 2004) In another review Field wrote of a randomised, controlled trial where partial liquid ventilation was used in mature infants with respiratory failure; he wrote that "Twenty-four subjects were randomized before recruitment was unexpectedly and inexplicably suspended. The results have never been published." (Field, 2002)

5. Perfluorocarbon liquid instillation and the effect on cerebral blood flow

As discussed above one of the concerns with the use of partial liquid ventilation in extremely preterm infants is its possible effect on cerebral blood flow and the potential to cause brain injury, especially during the initial dosing of perfluorocarbon into the lungs at the start of partial liquid ventilation. It may well be that any of the benefits of partial liquid ventilation are outweighed by an increase in the risk of brain injury.

Davies et al (Davies, 2010a; Davies, 2010b) studied the effects of perfluorocarbon dosing, when initiating partial liquid ventilation, on haemodynamics and cortical cerebral blood flow in preterm lambs. They showed that compared with preterm lambs continuing to be ventilated with conventional gas mechanical ventilation, lambs that received a dose of tracheal perfluorocarbon liquid at the start of partial liquid ventilation had an increase in their cortical cerebral blood flow. This could not be reasonably explained by any related changes in haemodynamics or oxygenation. The lambs that had 30 mL/kg of tracheal perfluorocarbon had a minimal increase in arterial carbon dioxide over the 30 minute observation period, although arterial carbon dioxide was not measured continuously and the difference was not statistically significant. Overall, three different loading doses of perfluorocarbon liquid were studied: 20, 30 and 40 mL/kg. (Davies, 2010a; Davies, 2010b) There were no significant haemodynamic changes during perfluorocarbon dosing in any of the three different doses in preterm lambs; and whilst the cortical cerebral blood flow was increased in all three groups there was no difference between groups.

Davies (Davies, 2011) reported further studies in a rabbit model designed to investigate the effects of different dosing strategies on cerebral blood flow. These studies confirmed that when the dose of perfluorocarbon was given into the trachea at the start of partial liquid ventilation cerebral blood flow increased. The cerebral blood flow increased regardless of the volume of the dose of perfluorocarbon; either 10 or 20 mL/kg. Furthermore, if the arterial carbon dioxide was closely monitored and the ventilation adjusted to maintain target arterial carbon dioxide, or volume-controlled ventilation was used, then there was no increase in cerebral blood flow. There was no significant advantage in varying the duration of administration of the dose of perfluorocarbon within the range from 10 to 20 minutes, although it is probably best to avoid giving the dose over 5 minutes or less. There was no benefit in giving the dose of perfluorocarbon through a secondary lumen at the distal tip of the endotracheal tube. With differences in cerebral blood flow there were also differences in some of the variables that may explain these differences. There were no statistically significant differences seen in arterial carbon dioxide. Although, on the two occasions where the differences in arterial carbon dioxide were almost statistically significant there were significant differences in either carotid flow or cortical cerebral blood flow or both. On one of those occasions the differences in pH were statistically significant and the changes in arterial carbon dioxide mirrored changes in pH, as would be usual. There were associations between increasing cerebral blood flow (or its variability) and factors measured that might explain those increases. In those situations where cerebral blood flow were increased there were also consistent increases in blood pressure and arterial carbon dioxide, and decreases in arterial oxygen. The increases in arterial carbon dioxide were associated with decreases in tidal volumes delivered during perfluorocarbon dosing. The most compelling reason that it was simply decreased tidal volumes that caused increased arterial carbon dioxide was that during those dosing strategies where the tidal volumes did not decrease (when using volume-controlled ventilation or closely targeting arterial carbon dioxide by adjusting peak inspiratory pressure) the arterial carbon dioxide did not increase.

Burkhardt et al (Burkhardt, 2002) report the only other study that investigated the effects of perfluorocarbon dosing on surrogate measures of cerebral blood flow: cerebral concentration of total and oxygenated haemoglobin using near infrared spectroscopy. The cerebral concentration of oxygenated haemoglobin decreased initially (at 1 minute) when 30 mL/kg was given extremely rapidly (over about 40 seconds), with return to baseline by 3 min and an increase after 5 min. There was no decrease with 30 mL/kg given slowly (over about 16 minutes) nor when 10 mL/kg was administered. The cerebral concentration of oxygenated haemoglobin and the total cerebral haemoglobin concentration increased when 30 mL/kg of perfluorocarbon was given but not with 10 mL/kg. Similarly in both 30 mL/kg groups the arterial carbon dioxide increased and arterial oxygen decreased but not in the 10 mL/kg group. There was no control group, therefore conclusions cannot be drawn about the effect of perfluorocarbon dosing compared with gas ventilation alone. The study design makes direct comparisons between the two volumes of perfluorocarbon given difficult because the doses were also given over different durations. Interpretation is also difficult as they did not measure cerebral blood flow directly, did not record and report real-time haemodynamic variables during the perfluorocarbon liquid dosing, and only reported changes in cerebral oxygenation at discrete time points. Burkhardt et al (Burkhardt, 2002) concluded that giving perfluorocarbon extremely rapidly (20-30 times faster than the fastest dosing studied by Davies (Davies, 2011)) is not recommended because of the decrease in cerebral blood flow (as determined by total cerebral haemoglobin concentration) during perfluorocarbon dosing.

From the results of the above studies we can surmise that perfluorocarbon should best be administered whilst either monitoring arterial carbon dioxide continuously during perfluorocarbon dosing and keeping it under tight control or using volume-controlled ventilation. This will prevent any decrease in arterial blood pressure or oxygenation, or any increase in arterial carbon dioxide. This in turn will prevent any disturbance of cerebral blood flow. The lowest possible dose-volume of perfluorocarbon should be used (e.g., 10 mL/kg or smaller, larger volumes may be acceptable but shouldn't be given too fast), and the dose should not be given over 5 minutes or less.

Given the availability of a suitable product, randomised controlled trials of partial liquid ventilation in neonates are both feasible and desirable. Now the design of such trials can incorporate some of the data from the studies summarised above and ensure that the dosing procedure is as safe as it can be for use in extremely preterm infants.

6. Conclusions

As is demonstrated by the above studies partial liquid ventilation has great potential to disturb cerebral blood flow and increase the risk of brain injury. If partial liquid ventilation is to be used in extremely preterm infants it should be safe. The best protection for the extremely preterm brain is to start partial liquid ventilation safely without disturbing cerebral blood flow. Given the potential for harm associated with perfluorocarbon dosing in the most susceptible of preterm infants it is encouraging to know that there are ways of giving perfluorocarbon that can mitigate any increase in cerebral blood flow.

7. References

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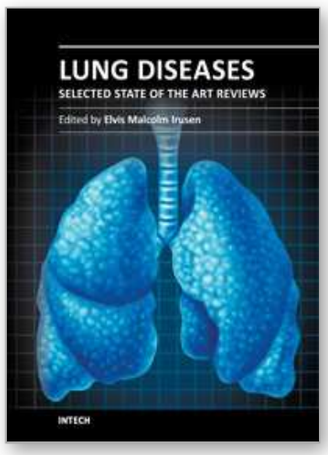

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